VERIFICATION OF A TRANSLATION

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declare as follows:

1. That I am well acquainted with both the English and Japanese languages

2. That the attached document is a true and correct translation made by me to the best of my knowledge and belief of:-

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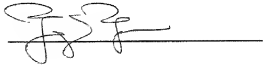
Signature of the translator



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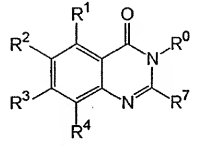
SPECIFICATION

[Title of the invention]

Method for preparing quinazolin-4-one compounds

[Scope of patent claim]

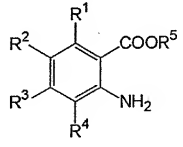
1. A method for preparing a quinazolin-4-one compound having the formula (4):



(4)

(in which R^0 represents a hydrogen atom or a hydrocarbyl group, and each of R^1, R^2, R^3, R^4 and R^7 independently represents a group optionally having a substituent which does not participate in the reaction, provided that R^1, R^2, R^3 and R^4 can form a ring in combination, and that there are no case in that both of R^0 and R^7 are hydrogen atoms);

which comprises reacting an anthranilic acid compound having the formula (2):



(2)

(in which each of R^1, R^2, R^3 and R^4 has the same meaning defined as above, and R^5 represents a hydrogen atom or a hydrocarbyl group);

with an organic acid compound having the formula (3):

$$(R^6O)_3CR^7 \qquad (3)$$

(in which R^6 represents a hydrocarbyl group, and R^7 has the same meaning defined as above);
in the presence of an amine compound having the formula (1):

$$R^0NH_2 \qquad (1)$$

(in which R^0 has the same meaning defined as above).

2. The method of claim 1 for preparing a quinazolin-4-one compound, in which R^6 is methyl or ethyl.

[Detailed description of the invention]
[Field of the invention]

This invention relates to a method for preparing quinazolin-4-one compounds from anthranilic acid compounds. The quinazolin-4-one compounds are useful compounds as starting compounds or intermediate compounds for preparing pharmaceutically active chemical compounds and agricultural chemical compounds.

[Prior art]

Hitherto known methods for preparing quinazolin-4-one compounds from anthranilic acid compounds are as follows:

(1) a method for preparing 6-iodoquinazolin-4-one by reacting 5-iodoanthranilic acid with formamidine acetate in ethanol for 20 hours, in which, however, it takes a long time to complete the reaction and it is necessary to use formamidine acetate, which is costly, in excess (see, Patent Document 1);

(2) a method for preparing a quinazolin-4-one by reacting anthranilic acid with formamide, in which, however, it is necessary to use formamide, which is terato-

genic, in excess (see, Non-patent Document 1); and

(3) a method for preparing quinazolin-4-one by reacting methyl anthranilate with formamide in the presence of ammonium formate, in which, however, it is necessary to react formamide, which is teratogenic, in excess at a high temperature and the product yield is low (see, Non-patent Document 2).

Patent Document 1: EP 1029853 (pp. 17, Examples)
Non-patent Document 1: Chem. Pharm. Bull., 46, 1926(1998) (pp. 1927, Experiments)
Non-patent Document 2: J. Org. Chem., 1953, 138 (pp. 145, Experiments)

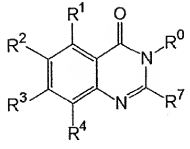
The above-mentioned methods have various problems and hence they are not suitable for industrial production of quinazolin-4-one compounds.

[Problem to be solved by the invention]

The present invention has an object to solve the above problems and to provide such an industrially suitable method for preparing quinazolin-4-one compounds that the quinazolin-4-one compounds can be easily prepared from anthranilic acid compounds with high yields under simple and moderate conditions.

[Means to solve the problem]

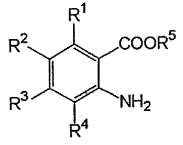
The object of the present invention is achieved by a method for preparing a quinazolin-4-one compound having the formula (4):



(4)

(in which R^0 represents a hydrogen atom or a hydrocarbyl group, and each of R^1, R^2, R^3, R^4 and R^7 independently represents a group optionally having a substituent which does not participate in the reaction, provided that R^1, R^2, R^3 and R^4 can form a ring in combination, and that there are no case in that both of R^0 and R^7 are hydrogen atoms);

which comprises reacting an anthranilic acid compound having the formula (2):



(2)

(in which each of R^1, R^2, R^3 and R^4 has the same meaning defined as above, and R^5 represents a hydrogen atom or a hydrocarbyl group);

with an organic acid compound having the formula (3):

$$(R^6O)_3CR^7 \qquad (3)$$

(in which R^6 represents a hydrogen atom or a hydrocarbyl group, and R^7 has the same meaning defined as above);

in the presence of an amine compound having the formula (1):

$$R^0NH_2 \qquad (1)$$

(in which R^0 has the same meaning defined as above).

[Embodiment of the invention]

The amine compound used in the reaction of the present invention is represented by the above formula (1). In the formula (1), R^0 represents hydrogen or a hydro-

carbyl group. Examples of the hydrocarbyl group are alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl; cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; aralkyl groups such as benzyl, phenethyl, and phenylpropyl; and aryl groups such as phenyl, p-tolyl, naphthyl, and anthryl. These groups can be in any isomer forms.

The aforementioned amine compound can be employed preferably in an amount of 1 to 100 moles, more preferably in an amount of 3 to 40 moles, per one mole of the anthranilic acid compound. The amine compound can be in any of gas, liquid, and solid. Otherwise, the compound can be employed in a solution in an organic solvent such as a polar solvent (e.g., alcohol).

The anthranilic acid compound used in the reaction of the invention is represented by the above formula (2). In the formula (2), each of R^1, R^2, R^3 and R^4 independently represents a group which optionally has a substituent and which does not participate in the reaction, and they are the same as or different from each other. Examples of them include hydrogen atom, alkyl groups, cycloalkyl groups, aralkyl groups, aryl groups, halogen atoms, hydroxyl group, alkoxy groups, alkylthio groups, nitro group, cyano group, carbonyl group, amino groups (which cannot be used as R^1), and carboxyl group (which cannot be used as R^4). R^1, R^2, R^3 and R^4 can form a ring in optional combinations.

The alkyl groups can be methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, or decyl. These groups can be in any isomer forms.

The cycloalkyl groups can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl.

The aralkyl groups can be benzyl, phenethyl, or phenylpropyl. These groups can be any isomer forms.

The aryl groups can be phenyl, p-tolyl, naphthyl, or anthryl. These groups can be in any isomer forms.

The halogen atoms can be fluorine, chlorine, bromine, or iodine.

The alkoxy groups can be methoxy, ethoxy, or propoxy. These groups can be in any isomer forms.

The alkylthio groups can be methylthio, ethylthio, or propylthio. These groups can be in any isomer forms.

The alkyl groups, cycloalkyl groups, aralkyl groups, aryl groups, alkoxy groups, alkylthio groups and amino groups (which cannot be used as R^1) can have a substituent. The substituent can be a substituent connected via a carbon atom, a substituent connected via an oxygen atom, a substituent connected via a nitrogen atom, a substituent connected via a sulfur atom, or a halogen atom.

Examples of the substituents connected via a carbon atom include alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, and hexyl, cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclobutyl, alkenyl groups such as vinyl, allyl, propenyl, cyclopropenyl, cyclobutenyl, and cyclopentenyl, heterocyclic groups such as pyrrolidyl, pyrrolyl, furyl, and thienyl, aryl groups such as phenyl, tolyl, xylyl, biphenylyl, naphthyl, anthryl, and phenanthryl, acyl groups (which can be acetallized) such as formyl, acetyl, propionyl, acryloyl, pivaloyl, cyclohexylcarbonyl, benzoyl, naphthoyl, and toluoyl, carboxyl groups, alkoxycarbonyl groups such as methoxycarbonyl and ethoxycarbonyl, aryloxycarbonyl groups such as phenoxycarbonyl, halogenated alkyl groups such as trifluoromethyl, and cyano group. These groups can be in any isomer forms.

Examples of the substituents connected via an oxygen atom include hydroxyl group, alkoxy groups such as methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, benzyloxy, piperidyloxy, and pyranyloxy, and aryl-

oxy groups such as phenoxy, tolyloxy, and naphthyloxy. These groups can be in any isomer forms.

Examples of the substituents connected via a nitrogen atom include primary amino groups such as methylamino, ethylamino, butylamino, cyclohexylamino, phenylamino, and naphthylamino, secondary amino groups such as dimethylamino, diethylamino, dibutylamino, methylethylamino, methylbutylamino, and diphenylamino, heterocyclic amino groups such as morpholino, thiomorpholino, piperidino, piperazinyl, pyrazolidinyl, pyrrolidino, and indolyl. These groups can be in any isomer forms.

Examples of the substituents connected via a sulfur atom include mercapto group, thioalkoxy groups such as thiomethoxy, thioethoxy, and thiopropoxy, and thioaryloxy groups such as thiophenoxy, thiotolyloxy and thionaphthyloxy. These groups can be in any isomer forms.

Examples of the halogen atoms include fluorine, chlorine, bromine, and iodine.

R^5 represents hydrogen or a hydrocarbyl group. Examples of the hydrocarbyl group are alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, and hexyl; cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; aralkyl groups such as benzyl, phenethyl, and phenylpropyl; and aryl groups such as phenyl, tolyl, naphthyl, and anthryl. These groups can be in any isomer forms.

The organic acid compound used in the reaction of the invention is represented by the above formula (3). In the formula (3), R^6 represents hydrogen or a hydrocarbyl group. Examples of the hydrocarbyl group are alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl; cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; aralkyl groups such as benzyl, phenethyl, and phenylpropyl; and aryl groups such as phenyl, p-tolyl, naphthyl, and anthryl.

Alkyl groups are preferred, and methyl and ethyl are more preferred. These groups can be in any isomer forms

R^7 has the same meaning defined as R^1, R^2, R^3 and R^4, but both of R^0 and R^7 are not hydrogens at the same time.

The aforementioned organic acid compound can be employed preferably in an amount of 1.0 to 15 moles, more preferably in an amount of 1.1 to 5.0 moles, per one mole of the anthranilic acid compound.

The reaction of the invention can be carried out in the presence or absence of a solvent. There are no specific limitations with respect to the solvents, under the condition that the solvent does not give adverse effect to the reaction. Examples of the solvents include alcohols such as methanol, ethanol, isopropyl alcohol, n-butyl alcohol, t-butyl alcohol, and n-pentanol, amides such as N,N-dimethylformamide and N-methylpyrrolidone, ureas such as N,N'-dimethylimidazolidinone, sulfoxides such as dimethyl sulfoxide, aromatic hydrocarbons such as benzene, toluene, xylene, and mesitylene, halogenated aliphatic hydrocarbons such as methylene chloride, chloroform, and dichloroethane, nitriles such as acetonitrile and propionitrile, and ethers such as diethyl ether, tetrahydrofuran, and dioxane. Preferred are alcohols, amides, and nitriles. More preferred are methanol, ethanol, N,N'-dimethylimidazolidinone, and acetonitrile. The solvents can be used singly or in combination.

The solvent can be employed preferably in an amount of 0 to 50 g, more preferably 0 to 20 g, most preferably 0 to 5 g, per 1 g of the anthranilic acid compound. The amount may vary depending on the conditions of the liquid reaction mixture such as homogeneousness and/or easiness for stirring.

The reaction of the invention can be carried out by mixing and stirring the amine compound, anthranilic acid compound, organic acid compound, and solvent under inert gas atmosphere. The temperature for the reaction is pre-

ferably in the range of 40 to 200°C, more preferably 50 to 150°C. There is no limitation on pressure for the reaction.

The final product, i.e., the quinazolin-4-one compound, can be isolated and purified after completion of the reaction by known methods such as extraction, filtration, concentration, distillation, recrystallization, and/or column chromatography.

[Examples]

The invention is further described by the following examples, but they by no means restrict the present invention.

[Example 1] Synthesis of 6-iodo-2-methylquinazolin-4-one

In a pressure resistant, 10 mL-volume stainless steel vessel, 1.00 g (3.8 mmol) of 5-iodoanthranilic acid, 2.47 g (15.2 mmol) of ethyl orthoacetate, and 5.0 mL (38 mmol) of 15 wt.% ammonia-methanol solution were heated at 125°C for 8 hours for performing a reaction. After the reaction was complete, the reaction mixture was cooled to room temperature and concentrated. To the concentrated reaction mixture was added 20 mL of water, to precipitate a crystalline product. The crystalline product was collected by filtration, to give 0.94 g (yield after isolation: 86%) of 6-iodo-2-methylquinazolin-4-one as a white crystalline product.

The 6-iodo-2-methylquinazolin-4-one had the following properties:

^{1}H-NMR (DMSO-d_6, δ(ppm)): 2.33 (3H, s), 7.36 (1H, d, J=8.5 Hz), 8.04 (1H, dd, J=8.6, 2.1 Hz), 8.35 (1H, d, J=2.0 Hz), 12.23 (1H, brs)

CI-MS (m/e): 287 (M+1)

[Example 2] Synthesis of 6-iodo-3-methylquinazolin-4-one

The procedures of Example 1 were repeated except

that 2.47 g (15.2 mmol) of ethyl orthoacetate and 5.0 mL (38 mmol) of 15 wt.% ammonia-methanol solution were replaced with 1.61 g (15.2 mmol) of methyl orthoformate and 5.0 mL (28 mmol) of 20 wt.% methylamine-methanol solution, respectively. There was obtained 0.98 g (yield after isolation: 90%) of 6-iodo-3-methylquinazolin-4-one as a brownish gray crystalline product.

The 6-iodo-3-methylquinazolin-4-one had the following properties:

^{1}H-NMR (DMSO-d_6, δ(ppm)): 3.94 (3H, s), 7.46 (1H, d, J=8.4 Hz), 8.09 (1H, dd, J=8.4, 1.8 Hz), 8.40-8.42 (2H, m)

CI-MS (m/e): 287 (M+1)

[Example 3] Synthesis of 6-iodo-2,3-dimethylquinazolin-4-one

The procedures of Example 1 were repeated except that 5.0 mL (38 mmol) of 15 wt.% ammonia-methanol solution was replaced with 5.0 mL (28 mmol) of 20 wt.% methylamine-methanol solution. There was obtained 0.83 g (yield after isolation: 73%) of 6-iodo-2,3-dimethylquinazolin-4-one as a white crystalline product.

The 6-iodo-2,3-dimethylquinazolin-4-one had the following properties:

^{1}H-NMR (DMSO-d_6, δ(ppm)): 2.56 (3H, s), 3.31 (3H, s), 3.52 (3H, s), 7.36 (1H, d, J=8.4 Hz), 8.04 (1H, dd, J=8.5, 1.8 Hz), 8.36 (1H, d, J=2.1 Hz)

CI-MS (m/e): 301 (M+1)

[Example 4] Synthesis of 6-iodo-2-phenylquinazolin-4-one

In a pressure resistant, 20 mL-volume stainless steel vessel, 1.00 g (3.8 mmol) of 5-iodoanthranilic acid, 1.13 g (15.2 mmol) of ethyl orthoacetate, 0.71 g (7.6 mmol) of aniline, and 10 mL of n-pentanol were heated at 125°C for 8 hours for performing a reaction. After the reaction was complete, the reaction mixture was

cooled to room temperature and concentrated. To the concentrated reaction mixture was added 20 mL of water, to precipitate a crystalline product. The crystalline product was collected by filtration, to give 0.87 g (yield after isolation: 66%) of 6-iodo-2-phenylquinazolin-4-one as a white crystalline product.

The 6-iodo-2-phenylquinazolin-4-one had the following properties:

^{1}H-NMR (DMSO-d_6, δ(ppm)): 7.51-7.58 (6H, m), 8.17 (1H, dd, J=8.7, 2.4 Hz), 8.39 (1H, s), 8.46 (1H, d, J=2.1 Hz)

CI-MS (m/e): 349 (M+1)

[Example 5] Synthesis of 6-iodo-2-benzylquinazolin-4-one

In a pressure resistant, 20 mL-volume stainless steel vessel, 1.00 g (3.8 mmol) of 5-iodoanthranilic acid, 1.13 g (15.2 mmol) of ethyl orthoacetate, 0.81 g (7.6 mmol) of benzylamine, and 10 mL of n-pentanol were heated at 125°C for 8 hours for performing a reaction. After the reaction was complete, the reaction mixture was cooled to room temperature and concentrated. To the concentrated reaction mixture was added 4 mL of 1 mol/L hydrochloric acid, to precipitate a crystalline product. The crystalline product was collected by filtration, to give 1.36 g (yield after isolation: 99%) of 6-iodo-2-benzylquinazolin-4-one as a white crystalline product.

The 6-iodo-2-benzylquinazolin-4-one had the following properties:

^{1}H-NMR (DMSO-d_6, δ(ppm)): 3.32 (2H, s), 7.32-7.36 (5H, m), 7.49 (1H, d, J=8.7 Hz), 8.11 (1H, d, J=2.1 Hz), 8.42 (1H, d, J=1.8 Hz), 8.61 (1H, s)

CI-MS (m/e): 363 (M+1)

[Effect of the invention]

The present invention can provide an industrially suitable method for preparing quinazolin-4-one compounds.

According to the invention, quinazolin-4-one compounds can be easily prepared from anthranilic acid compounds with high yields under simple and moderate conditions.